University of Alberta

Multiple Myeloma and Hemoglobin Prior to Autologous Bone Marrow Transplant

by

Nanette Catherine Cox-Kennett

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Abstract

Autologous bone marrow transplant is the standard of care for multiple myeloma. However, long term cure has not been achieved. The prognostic importance of hemoglobin (hgb) at time of diagnosis and immediately prior to transplant has not been clearly defined. The purpose of this longitudinal cohort analysis is to identify the role that a higher hemoglobin at diagnosis and immediately prior to transplant (>110 g/L) has in multiple myeloma survival after autologous bone marrow transplant. A retrospective chart analysis of 79 patients diagnosed with multiple myeloma and receiving autologous bone marrow transplant at a large oncology center was undertaken. Overall survival at 5 years was 49%. Median overall survival for patients with hgb less than 110 g/L at diagnosis (n= 43), was 4.9 years versus 5.6 years hgb >= 110 g/L (p. 95). Patients with hgb level less than 110 g/L at time of transplant had a median survival of 4.6 years versus those with hgb >= 110 g/L at transplant, surviving 5.6 years (p=.45). Patients with a higher hemoglobin level did experience decreased length of hospital admission, improved time to platelet recovery, and a trend towards improved myeloid engraftment. Given the opportunity to improve patient outcomes and reduce costs to the health care system associated with these interventions and inpatient days, future investigations are warranted

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Chapter One

Multiple myeloma is a relatively uncommon cancer. A great deal of research has taken place to identify best treatment options as well as pinpoint specific pathophysiologic markers which will aide in predicting a patient's response to therapy and length of life. One of these markers is the serum hemoglobin level at diagnosis as many patients initially present with anemia. Hemoglobin level at diagnosis has been utilized as part of the staging criteria for myeloma. A higher hemoglobin level at diagnosis was found to be predictive for survival in two research studies for patients receiving autologous bone marrow transplant. (Gertz, 1999; Child, 2003). However, other studies have not found any survival benefit associated with higher hemoglobin at diagnosis (Palumbo, 1999). These findings show that the role of hemoglobin at diagnosis as a predictor of survival post autologous bone marrow transplant is far from clear.

Clinicians have also speculated that hemoglobin levels improve after myeloma treatment pre-transplant, but no peer-reviewed studies supporting this claim were identified. Thus any benefit that might be associated with this improvement is also unknown. This thesis describes a longitudinal cohort study that was undertaken to address this knowledge gap. Before proceeding with a discussion of hemoglobin and transplant, a review of the etiology, incidence, risk factors, pathophysiology, and diagnostic criteria of multiple myeloma will be presented.

Etiology, Incidence and Risk Factors

Multiple myeloma is a relatively uncommon cancer of the white blood cells, specifically the activated B cells. Skeletal evidence has been found for its existence in Egyptian mummies (Zaidi & Vesole, 2001) but it was not until 1873 that it was first

designated as a disease with six cardinal features: multiple skeletal tumors, pathological fractures, Bence Jones proteins, back pain, anemia and renal insufficiency (Kyle, 1998).

A diagnosis of multiple myeloma (MM) will be made in approximately 1850 persons in Canada this year (Canadian Cancer Society/National Cancer Institute, 2005). Approximately 185 of these cases will be in Alberta. MM affects 5 of every 100,000 males in Canada and 3 of every 100,000 females, each in their latter years of life (Canadian Cancer Society/National Cancer Institute of Canada, 2005). Median age at diagnosis is 71 with very few patients presenting under the age of 40 (Zaidi & Vesole, 2001). Some ethnic groups, such as African Americans, have a higher risk for developing MM. Native Pacific Islanders have a moderate risk of developing MM while Asians have the lowest risk (Kyle, 1998).

The exact etiology of MM is unknown. No hereditary basis has been found for this disorder. Risk factors for developing MM are believed to be related to chronic immune stimulation and autoimmune disorders which are linked to chronic antigenic stimulation of the immune system and thus to the pathogenesis of the disease (Sheridan, 1996). It is hypothesized that B cells become damaged through exposure to chemicals, viruses, or radiation and that this gives rise to malignant plasma cells (also known as myeloma cells). The myeloma cells overproduce themselves and do not succumb to modulators of regular apoptosis. Occupational hazards for MM are found within the wood, metal, rubber, textile and petroleum industries. Exposure to toxic substances including ionizing radiation, pesticides, herbicides, dioxin, and Agent Orange (Sheridan, 1996; Zaidi & Vesole, 2001) as well as viruses, such as HIV, Kaposi's sarcoma-

associated herpes virus and human herpes virus 8 (Rettig & Ma, 1997; Zaidi & Vesole, 2001), is associated with the development of MM.

Pathophysiology

To fully comprehend multiple myeloma, an understanding of hematopoiesis is required. In their review of multiple myeloma, Devenney and Erickson (2004) summarize hematopoiesis with the following:

> All immune cells begin in the pluripotent stem cell, which has the ability to replicate or differentiate into either lymphoid or myeloid lineages. The myeloid lineage further differentiates into platelets, neutrophils, eosinophils, and basophils; the lympohoid stem cell divides into either T or B lymphocytes. B lymphocytes mature into immunoglobulin—producing plasma cells which are responsible for humoral immunity. (p.401).

In contrast to leukemia which is a proliferation of immature white blood cells (myeloid or lymphoid), multiple myeloma is characterized by uncontrolled growth and failure of apoptosis of mature plasma cells (or B-lymphocytes). These malignant mature cells continue to secrete plasma proteins (immunoglobulins), which crowd the serum.

Each immunoglobulin consists of four polypeptide chains, two light chains (kappa and lambda) and two heavy chains (either IgG, IgA, IgM, IgE, IgD). When examining the urine or serum of a patient with multiple myeloma, an elevation in one monoclonal protein, called the "M-protein" or myeloma protein, is elevated. This protein, in turn, will reflect the immunoglobulin subtypes. These subtypes are present with variable

frequency: IgG 55%, IgA 26%, light chain (or Bence Jones) 14%, non-secreting 1-2%, IgD 1-2%, and IgM/IgE or biclonal (rare) (Malpas, 1998; Harousseau, 2002).

Presentation, Diagnosis, and Prognostic Factors

Upon first presentation, a patient with multiple myeloma (MM) may have a myriad of symptoms or no symptoms at all. The most common presenting concern is bony pain. The deluge of plasma cells release osteoclast stimulating factor causing destruction of the bone particularly in the vertebral column, ribs, skull, pelvis and femora. Skeletal x-ray may reveal osteolytic lesions giving the bone a Swiss-cheese appearance. There may also be micro-compressions of the vertebral column resulting in lost height or spinal cord compression (Harousseau, 2002). Osteoblastic response is suppressed and a secondary hypercalcemia with its symptoms of nausea, confusion, polyuria, constipation and excessive thirst may be present (Malpas, 1998; Harousseau, 2002).

Patients with myeloma may be fatigued and suffer from recurrent infections. Renal insufficiency is also common (1/3 of patients) as the excess immunoglobulins congest in the collecting tubules and dialysis may be required (Zaidi & Vesole, 2001). These same excess proteins cause hyperviscosity syndrome evidenced by oral bleeding, epistaxis, blurred vision, retinal changes, paresthesias, and congestive heart failure. Although rare, hyperviscosity affects up to 4% of patients with IgG type and up to 10% of IgA type of MM (Devenney & Erickson, 2004). In up to 15% of myeloma patients, amyloidosis occurs characterized by the deposition of excess proteins tissues other than the kidney. Protein deposits can be found within the tongue, gastrointestinal tract, heart, skin, skeletal muscle and carpal ligaments (Haroussea, 2002).

Most myeloma patients are asymptomatic and the diagnosis is made upon routine physical examination. Approximately 3% of persons over the age of 70 years will have an elevated monoclonal protein without other symptoms of myeloma (Kyle & Rajkumar, 2002). These conditions, monoclonal gammopathy of unknown significance (MGUS) or indolent/smoldering myeloma (SMM), do not require immediate treatment. Routine clinical monitoring is necessary, however, as 1% per year of MGUS will transform to myeloma and SMM is known to progress at a median of 2 years (Devenney, & Erickson, 2004; Harousseau, 2002). Additionally, up to 3% of patients will present with a solitary plasmacytoma (a growth of plasma cells outside the marrow) requiring radiotherapy alone for curative intent (National Cancer Institute, 2005).

The initial diagnostic testing for a patient suspected of having MM will typically include a complete blood count, calcium, serum creatinine, quantitative immunoglobulins, bone marrow biopsy, and serum/urine protein electrophoresis, along with other routine testing. A skeletal survey (skull, ribs, vertebrae, pelvis, shoulder girdle and long bones) is also required. Immunofixation will determine the sub-type of excess heavy or light chain protein. Serum Beta 2 (β_2) microglobulin is also measured as it is a good marker for disease burden. This protein, found on the surface of nucleated cells, is released into circulation with high tumor burden. β_2 levels have proven to be a highly significant predictor for survival, response to chemotherapy, and subsequently for estimating tumor mass (Bataille, Grenier, & Sany, 1984). For a summary of these tests and expected results please see Table 1. A needle aspirate of solitary lytic lesions, extramedullary tumors or enlarged nodes may also be necessary.

Factors associated with a good prognosis include: normal hemoglobin (hgb), absence of renal dysfunction/hypercalcemia, absence/few lytic bone lesions, normal immunoglobulin levels in serum and urine, normal serum lactic dehydrogenase, serum $Beta_2$ microglobulin <3mg/L, and c-reactive protein < 0.4mg/dL (a surrogate marker for the plasma cell growth factor interleukin 6) (Grethlein, 2004; Davies, Anderson, Dorfman, & Skarin, 2003; Durie et al, 1990). Low interleukin 6, plasma cell labeling index less than 1%, absence of chromosome 11 and/or 13 abnormalities, absence of *kras* mutations and p53 deletions, are also associated with improved survival (Zaidi & Vesole, 2001; Tricot et al, 1995).

Table 1

Diagnostic Evaluation (Grethlien, 2004; Harousseau, 2002)

Diagnostic testing	MM Results
CBC	Anemia, thrombocytopenia, leucopenia
Total protein	Elevated
Calcium	Elevated
Creatinine	Elevated
Serum Immunoglobulins	Elevated IgG, IgA, IgD, or IgE.
Bone marrow biopsy	Monotypic plasma cells > 10%, cells may appear more immature with less differentiated nucleus, diffuse chromatin and one or several nuclei

Diagnostic testing	MM Results
Skeletal survey	Lytic lesions, pathological fractures
Serum protein electrophoresis	Monoclonal spike (>0.5g/dL)
24 hr urine protein electrophoresis	> 1g/24hr urine protein with monoclonal spike
Serum β 2 microglobulin	Elevated >2.5 ug/ml
C-reactive protein (surrogate marker for the plasma cell growth factor interleukin 6)	Elevated
Cytogenetic testing	Chromosome abnormalities (chromosome 11 deletions, monosomy 13/deletion 13q/ translocations of 13q)

The first six criteria in Table 1 have been incorporated into the staging system for myeloma (see Table 2). Using this staging system, the majority of patients present at clinical Stage Three. Estimating survival for this group is difficult. In 2005, a new international staging system was proposed (see Table 3) utilizing serum beta microglobulin levels and serum albumin at diagnosis (Griepp et al, 2005). These staging criteria have been widely accepted and will be the basis for all future clinical staging starting in 2005.

Table 2

Durie & Salmon Staging Criteria (National Cancer Institute, 2003).

Stage	Hgb g/L	Calcium mg/dL	Presence of lytic bone lesions	IgG (g/L)	IgA (g/L)	Urinary kappa or lambda (g/24 hours)
1 (all criteria)	> 100	2.1 – 2.57	None	< 0.5	< 0.3	< 4
2	85 - 100	2.58 – 2.96	1 - 3	0.5 –0.7	0.3 – 0.5	4 – 12
3 (at least one)	< 85	> 2.96	> 3	>0. 7	> 0.5	> 12

Note. Subclassification: Class A: Creatinine less than 207 umol/L

Class B: Creatinine greater than or equal to 207 umol/L

Table 3

2005 International Staging System (Griepp, et al; 2005)

Stage		Median survival
1	β_2 microglobulin<3.5mg/L Albumin >= 3.5g/dL	62 months
2	β_2 < 3.5 mg/L with albumin < 3.5 g/dL OR β_2 3.6 – 5.4 mg/L regardless of albumin	44 months
3	β_2 >= 5.5 mg/L	29 months

Myeloma and Anemia

A low serum hemoglobin (hgb) level (hgb < 85 – 140 g/L) at the time of diagnosis is known to reflect a poorer prognosis for many cancer patients, but the mechanism of action is not well understood (Caro, Salas, Ward, & Goss, 2001). The definition of anemia is widely varied within the literature. For the duration of this paper, hemoglobin level less than 110 g/L shall be classified as anemia. Severe anemia shall be classified as hemoglobin level less than 85 g/L. Up to 30% of patients with cancer have been reported to suffer from anemia related to the disease process itself or to its treatment of chemotherapy and/or radiotherapy (Caro et al., 2001). Anemia increases the relative risk of death by as much as 65% within the general oncology population (Caro et al.). In the early 1970's, up to 62% of patients diagnosed with multiple myeloma presented with anemia (Kyle, 1998).

The factors believed to cause anemia in patients with MM include: displacement of normal marrow by plasma cells, suppression of erythropoiesis leading to erythropoietin deficiency, renal failure, effects of chemotherapy and radiation, hemodilution, decreased red cell life span, myelodysplasia/acute leukemia, hypersplenism, iron deficiency, and megaloblastic anemia (Ludwig & Fritz, 1996; Meharchand, 1998). Due to advances in early detection, normochromic normocytic anemia is now typically found in only 50% of multiple myeloma patients at diagnosis. Of these, severe anemia (hgb <85 g/L) is found in 8 -19% of these patients (Meharchand, 1998). Initial improvements in hgb level are achieved upon partial or complete response to chemotherapy as well as treatment of any other underlying cause. Anemia will progress and persist in patients who are resistant to therapy.

Anemia can lead to various organ dysfunctions including tachycardia, dyspnea, cardiac decompensation, changes in cognitive status, decreased libido, kidney function, and impairment in the immune system, as well as decreased quality of life (Egerer, Harter, Karthaus, Ho, & Goldschmidt, 2003). Given these serious issues, studies designed to achieve and maintain a hgb level greater than 110 g/L are critically important. Potential outcomes could include improved quality of life, increased ability to comply with therapy, decreased transfusion frequency, decreased transfusion related side effects, and reduced infections (Egerer, et al). Reducing transfusion requirements also diminishes the risk of iron overload, which is important in the MM population given the hyperviscosity inherent in this disease.

Myeloma Survival

A diagnosis of multiple myeloma had a dim forecast of only 7 months survival prior to the use of chemotherapy (National Cancer Institute, 2005). Survival has been extended up to several years now, given current therapies, but a cure remains beyond our current medical grasp. Ten year overall survival is approximately 3% (National Cancer Institute, 2005). With standard chemotherapy, patients diagnosed with stage one myeloma have been reported to have a median survival of up to 191 months, stage two from 11 – 54 months, and stage three from 5 – 34 months (National Cancer Institute, 2005). It is estimated that 1250 myeloma patients will die in 2005, and that approximately 95 of these deaths will be in Alberta (Canadian Cancer Society/National Cancer Institute of Canada, 2005).

Bisphosphonates are used in the symptomatic management of osteolytic lesions and hypercalcemia associated with multiple myeloma. Regular monthly use of

bisphosphonates has reduced the frequency of pathological fractures, bony pain, spinal cord compression and the need for palliative bone radiotherapy. While this treatment has not been given with any curative intent, it has also been shown to improve survival from 14 months to 24 months in MM patients with Stage Three disease (Berenson, 1998).

Standard treatment for multiple myeloma includes high dose combination chemotherapy followed by peripheral blood stem cell rescue or autologous (self – to-self) bone marrow transplant (BMT). Although not a cure, autologous transplant are known to improve survival rates by up to 23 months and are currently a mainstay in the arsenal for treatment (Attal et al, 1996; Child et al., 2003; Gertz et al., 1999). The time between initial diagnosis and transplant can be extensive ranging from 4 to 38 months (Gertz et al, 1999). This time is often used to correct the underlying anemia found in up to 50% -75% of myeloma patients (Meharchand, 1998; Zaidi & Vesole, 2001). The literature is not currently definitive regarding the role that increased hemoglobin levels at diagnosis plays in survival for multiple myeloma patients receiving autologous bone marrow transplant. As mentioned previously, Gertz (1999) and Child (2003) confirmed that higher hemoglobin was linked with increased survival however Palumbo (1999) found no correlation.

Correction of anemia in MM patients can include transfusion support or human recombinant erythropoietin alpha (rHuEPO) to stimulate erythrocyte production. Xenocosta and colleagues (2003) have found that an improved hgb level immediately prior to bone marrow transplant can be correlated with prolonged survival independent of other risk factors. However, this study reflects allogeneic bone marrow transplants and there were no myeloma patients within the patient population. It is unknown if this same

increase in survival would be found within the autologous bone marrow transplant population. Additionally, the change (if any) in hgb status from initial myeloma diagnosis to the time immediately prior to autologous bone marrow transplant (BMT) and any impact this has on survival is not well documented in the literature.

A longitudinal cohort study examining the impact of hgb level at the time of autologous bone marrow transplant is proposed to address this gap in the literature. While hgb level at diagnosis has been found to be a prognostic indicator for survival within the multiple myeloma population in some studies, hgb level prior to transplant (outside of the allogeneic bone marrow transplant patient population), has yet to be explored.

Purpose of the Study

The literature has revealed a gap in knowledge regarding relationships between hgb levels immediately prior to transplant and survival in multiple myeloma patients undergoing autologous bone marrow transplant. The purpose of this study is to address this gap. The role that hemoglobin level at diagnosis plays in survival is also not definitively answered within the literature. This study will explore the relationship between hgb levels at diagnosis as well as immediately prior to transplant and length of survival in multiple myeloma patients receiving autologous bone marrow transplant at a large oncology treatment facility, serving all of northern Alberta (Cross Cancer Institute, Edmonton, Alberta).

Research question

Among individuals diagnosed with multiple myeloma, the research questions are:

1) What is the relationship between hgb level at diagnosis and survival?

2) What is the relationship between hgb level at the time of transplant and survival?

Definition of Terms

Anemia (moderate): Hgb level less than 110 g/L.

Anemia (severe): Hgb level less than 85 g/L

Date of diagnosis: First visit to Cross Cancer Institute or first consult to referring hematologist.

Hemoglobin level: Hemoglobin measured in g/L.

Survival: Time in days from transplant (day 0 being administration of conditioning chemotherapy) to date of death.

Neutrophil engraftment: neutrophils count as absolute WBC > 1.0 or neutrophil count $>0.5 \times 10^9$/l for 3 consecutive days.

Platelet engraftment: platelet count greater than 50×10^9/l without transfusions.

Significance of the Study

This study addresses an important gap in the literature. Xenocosta showed that hgb level at the time of transplant increased survival in the allogeneic population. The majority of individuals diagnosed with MM, however, are not eligible for this treatment option, due to their age and other health concerns. These individuals are currently treated with autologous stem cell transplants, however, and they respond modestly to this treatment. If the findings of this study show that there is a relationship between hgb level at the time of transplant and survival, it will lay important groundwork for further

research in this area. The results will be shared with the oncology community in an effort to advance transplant knowledge and guide future research.

Chapter Two

Literature Review

In an attempt to elucidate what is currently known regarding multiple myeloma, serum hemoglobin and the autologous bone marrow transplant experience, an on-line search to identify the current status of the literature on this topic was undertaken. The databases MEDLINE, EMBASE, CINAHL, were searched for articles published between 1980 to present using the following keywords: multiple myeloma, autologous bone marrow transplant, autologous hematopoietic stem cell transplant, hemoglobin and survival, cancer and survival, multiple myeloma and erythropoietin. Citations from relevant articles were also reviewed.

Current MM Treatment

Myeloma patients that remain asymptomatic with normal hgb levels, calcium, renal function and no bony lesions may remain stable for long periods of time and early treatment has shown no proven benefit to overall length of survival (Hjorth et al, 1993; Riccardi et al 2000; He, 2005). Traditional protocol therapies for symptomatic myeloma have shown that no one ablative regimen is optimal (Myeloma Trialists' Collaborative Group, 1998; National Cancer Institute, 2005). Unfortunately, multiple myeloma is a disease marked by resistance to currently available chemotherapy and relapse is inevitable. Research regarding novel therapies producing higher incidence of complete response at initial diagnosis as well as salvage regimens for those patients refractory to current treatments is ongoing.

Kumar, Loughran, Alsina, Durie and Djulbegovic (2003) encapsulate the evolving approach to myeloma management excellently in their systematic review of

over 156 randomized controlled trials and three meta-analyses. To summarize, cyclophosphamide is superior to placebo (median survival 49 weeks vs 15 weeks), melphalan and prednisone (MP) combinations are better than melphalan as a single agent (median survival improved by 6 months), and combination chemotherapy regimens are superior to MP with a response rate 60% vs 53% (p.00001). Finally, delayed versus immediate treatment does not influence survival.

Autologous Bone Marrow Transplant

Failure of conventional or standard chemotherapy to prolong the disease free state has led investigators to test the effectiveness of much higher doses of myelosuppressive medications. As early as 1983, McElwain & Powles investigated the use of high dose melphalan and noted a 50% complete response rate at the expense of severe myelosuppression and a high toxic death rate. Barlogie and colleagues (1986) followed up on this premise for a small sample (N=23) of patients with primary refractory or MM patients who had originally failed to respond to initial chemotherapy. They again noted the severe and prolonged myelosuppression and toxicities in their first 16 patients receiving high dose melphalan. They then modified the protocol to include a hematopoietic stem cell rescue after the high dose chemotherapy for the next 7 patients. Stem cells were collected prior to beginning the high dose protocol. These harvested hematopoietic stem cells or bone marrow promoted recovery (median survival 6 months versus 14+ months with stem cell support).

Allogeneic Bone Marrow Transplant

This form of autologous bone marrow/stem cell transplant following high dose chemotherapy has been the focus of many prospective trials. Up until this point,

allogeneic transplant (unrelated or related donor) was the only transplant option for younger multiple myeloma patients free from comorbidities but the risks associated with the highly toxic preparative regimen are significant. Transplant related mortality has been reported to be anywhere from 18 to 42% (Arora et al, 2005; Ballen, 2005). Combined with the risk of graft versus host disease, these toxicities leave this option open to the fewer than 3% of MM patients presenting at less than 40 years of age with a well-matched donor (Davies et al., 2003). Prolonged remission up to 16 years has been observed (Enitza & Sadovsky, 1999) and for those patients who survive past the first 100 days from transplant, four year overall survival is up to 64 % (Arora, 2005).

Autologous BMT Process

With allogeneic transplant an option for few patients, autologous transplant with its reduced toxicity (less than 3-5% toxic deaths) is currently considered an alternative for many (Devenney & Erickson, 2004). Many different regimens utilizing different combination chemotherapy regimens to induce remission and then fully ablate the marrow have been explored with varying degrees of success (see Table 4). Results of recent trials have produced steady change within the transplant process and sometimes uncertainty as to best practice (Imrie, Esmail, Meyer, and Cancer Care Ontario, 2002). A review of the literature reveals the following steps in the transplant process (see Table 4):

1) Induction or debulking with repetitive cycles of combination chemotherapy for patients upon initial diagnosis to achieve an in vivo purging effect. Original trials collecting autograft later upon relapse or after treatment failure resulted in high myeloma contamination.

Exposure to multiple chemotherapy regimens (especially alkylating agents) prior to transplant reduces survival (Fermand, 1993).

2) Use of slightly myelosuppressive therapy to mobilize stem cells into over production enhancing the pheresis collection cell count.

3) Use of growth factors to push stem cells into production and systemic circulation thereby enhancing graft cell count.

4) Collection of peripheral blood stem cells or, alternatively, of bone marrow if not able to collect a minimum of 2×10^6/kg CD34+ cells through pheresis. Myeloma cells lack CD34+ expression (Dyson, 2000). Peripheral stem cells are proven to reduce time to neutrophil and platelet engraftment over marrow and are the collection of choice. Purging the graft of myeloma cells or specifically selecting out only CD34+ cells has not proven to improve survival (Lemoli, 2000; Stewart, 2001; Vescio, 1999).

5) Myeloablative chemotherapy plus or minus total body irradiation followed by reinfusion with stem cells/bone marrow. Growth factors post stem cell infusions have been utilized to improve time to cell engraftment. Achieving a complete response (as defined by researcher – minimally an absence of monoclonal protein) enhances survival (Imtir, Esmail, & Meyer, 2002). The use of interferon alpha as maintenance therapy remains debated.

BMT Trials

In 1996, Attal et al. published the results of the first randomized trial ($N = 200$) examining autologous transplant for previously untreated multiple myeloma compared to conventional combination chemotherapy. After four to six cycles of vincristine, carmustine, doxorubicin, cyclophosphamide (VMCP) alternating with vicristine, melphalan, cyclophosphamide and prednisone (BVAP), patients progressed to high dose melphalan and total body irradiation (TBI) as preparation for transplant. Median time from diagnosis to transplant was 5.5 months (range 4-11 months). The range of hgb levels at presentation is not disclosed although a mean of 110 g/L is reported. Intervening therapy, if any, in the five months prior to transplant for patients who may have been anemic upon presentation was not discussed. Complete responses were obtained in 5% of patients in the conventional treatment arm and 22% in the high dose therapy/bone marrow transplant rescue arm. Estimated 5 year survival in the conventional arm was 12% versus 52% with transplant. These results were confirmed by a later trial published by Child in 2003 with 54.1 months survival for autologous transplant versus 42.3 months standard chemotherapy. A second transplant for those patients having sufficient stem cells collected and not experiencing a complete response after the first transplant has also been shown to prolong survival to 48 months for single versus 58 for months double transplant (Attal, 2003). It has been concluded that high-dose therapy with autologous stem-cell rescue is an effective first-line treatment improving response rate, event free survival and overall survival in patients with multiple myeloma (Attal, et al., 1996; Child, 2003).

Management of Anemia Associated with MM

Relief from anemia upon diagnosis may be achieved with the treatment of the myeloma itself through chemotherapy, a mainstay in the battle for continued disease free survival. Alternatively, many myeloma patients presenting with symptomatic anemia receive treatment to correct underlying causes (e.g. iron or folate deficiencies), allogeneic transfusion support, or human recombinant erythropoietin alpha (rHuEPO). Erythropoietin is a major growth factor stimulating proliferation and differentiation of erythroid progenitor cells. It also amplifies production of red blood cells through inhibition of apoptosis (programmed natural cell death) in precursor cells (Ludwig & Fritz, 1996). Normally produced by the cells within the kidney and minimally from liver macrophages, erythropoietin production is stimulated by tissue perception of hypoxia and lower hematocrit. Erythropoietin secretion has been found to be inadequate to the degree of anemia in 50% of multiple myeloma patients with severe anemia (Beguin et al., 1992 as cited in Meharchand, 1998). The exact cause for this low erythropoietin level is unknown, but it likely reflects the poor erythropoietin production by the kidney, which is inundated with monoclonal proteins released from the proliferative monoclonal plasma cells.

If a deficit in erythropoietin production is the sole underlying mechanism for myeloma anemia, it stands to reason that correction through the use of synthesized erythropoietin could correct the process. In their summary of several rHuEPO trials within the multiple myeloma population, Caro et al. (2001) demonstrated 55-78% response rates (i.e. increased hgb levels beyond 20g/L) regardless of tumor stage and renal insufficiency. Time to response varied from two weeks to two months. The lack of

complete response indicates the hemoglobin deficit is multifaceted and there must be other underlying causes for myeloma associated anemia beyond the deficit in erythropoietin. Correction of anemia is relevant in this population as maintaining hgb level throughout therapy is of critical importance. Dose reductions of chemotherapy up to 20%, which are common in oncology practice due to myelosuppression, can lead to a 50% reduction in response rate thereby reducing survival (Henry, 1997). While anemia may initially improve with reduced tumor burden, benefits may be impeded by chemotherapy and radiation treatments, both of which inhibit hematopoiesis. The battle against anemia in multiple myeloma is therefore, multifactorial.

Possible Benefits of Increased Hemoglobin

As Attal's research revealed a survival advantage for autologous transplantation in myeloma, the timing for transplant was then scrutinized. Gertz (1999) examined early (i.e. after a few initial cycles of chemotherapy) versus late transplantation (only upon disease progression after multiple cycles of chemotherapy). Results indicated no significant survival benefit from either treatment regimen. Using multivariate Cox analysis, the authors showed that factors predicting survival for those patients receiving late transplantation ($N = 118$) included hgb level at diagnosis ($p = 0.01$) as well as $ß_2$ microglobulin levels ($p = 0.006$). Interestingly, hgb level at diagnosis ranged from 4.5 – 159 g/L with nearly one third of patients presenting with hgb levels less than 100 g/L. Median time from diagnosis to transplant was 38 months. While low hgb level may reflect the level of tumor burden, the time delay to transplant also presented a greater opportunity to correct underlying anemia. Any change in hgb status in the period between diagnosis and transplant is not mentioned. For a complete summary of reported hgb

levels at diagnosis in autologous bone marrow transplant published research (see Table 4).

Table 4

BMT Hemoglobin at diagnosis in literature

Author	Year	Hemoglobin	Comments
Schiller	1995	___	Median # of PRBC transfusions 7 (range 2 – 37)
Bensinger	1996	___	RBC transfusions PBSC 6 (range 2-20) PBSC & Marrow 7 (3 –24) Marrow 8 (2-21)
Attal	1996	110 +/- 20	___
Barlogie	1997	34% Hgb < 100	___
Fermand	1998	Hgb 107 +/- 22 15% Hgb < 100 early BMT 18% Hgb< 100 late BMT	___
Vescio	1999	___	Median # transfusions 4
Palumbo	1999	___	Hgb < 100 at diagnosis not predictive for survival (p= 0.84)
Gertz	1999	Hgb 45 – 159 Median 111 32% hgb <- 100 g/L 70% hgb < 120 g/L	Univariate and multivariate analysis hgb predicted for survival (p = 0.01)
Lenhoff	2000	35% hgb < 100 g/L	___

Author	Year	Hemoglobin	Comments
Blade	2000	Hgb < 100 g/L 39% for BMT vs 52% for chemo alone	___
Olivieri	2001	___	Median # transfusions 2
Badros	2001	30% Hgb < 100 g/L	___
Moreau	2002	Median 112 g/L Range 60 – 162 g/L	___
Moreau	2002	Median hgb 110 Range 54 – 168 g/L	Median # transfusions 2
Child	2003	Male 54% hgb < 115 g/L Female 40% hgb < 95 g/L	Cox regression analysis Increased survival with hgb > 90 g/L at diagnosis.
Attal	2003	10.7 +/- 2.2	___
Murakami	2004	90 g/L median for controls 107 g/L for BMT	___
Kumar	2004	Median 108 g/L Range 65 – 1.1 g/L	___

Modifying Attal's study, Child et al. (2003) completed a randomized trial of 407 previously untreated myeloma patients utilizing the same combination chemotherapy regimen, although only for 3 cycles prior to transplant. High dose melphalan with or without total body irradiation (dependent upon renal function) was used for conditioning.

Included among the randomization factors was the use of total body irradiation as well as hgb level less than 90 g/L. At the time of randomization, 47% of males had hgb levels less than 115 g/L and 38% of women less than 95 g/L. Once again, changes to hgb levels prior to transplant and any therapies utilized to support anemic patients are not discussed. This may be due to a lack of significant change in these levels and/or because no therapies were provided. Overall survival was 54.1 months in the transplant group compared to 42.3 months in the standard chemotherapy group. Predictors of survival included hgb > 90 g/L as well as creatinine less than 1.7 mg/dL and low $beta_2$ microglobulin level. The advantage of high dose chemotherapy followed by stem cell support is evident, particularly if hgb level is greater than 90 g/L.

Both Child et al. (2003) and Gertz (1999) discuss hgb level at diagnosis as a predictor for survival in multiple myeloma patients receiving autologous bone marrow transplant. Child (2003) reports that survival rates were higher among patients with hgb level greater than 90 g/L. The length of survival improvement is not discussed. It seems reasonable to assume patients presenting with hgb level of 45 g/L received some form of supportive therapy and that levels changed in the many months prior to transplant. With delays from diagnosis to transplant ranging from 3 to 38 months, it would be interesting to know if hgb levels immediately prior to transplant significantly predicted survival.

Further evidence that hgb level may influence transplant survival can be drawn from Littlewood et al. (2001). Recognizing that hgb level influenced oncology patients survival, this trial of 375 patients (65% had myeloma) examined the effect of erythropoietin in raising levels and subsequent survival impact. Hemoglobin values were increased to a mean of 120 g/L over a maximum 28 weeks. The myeloma/lymphoma

population had a mean increase of 22 g/L. Median survival with conventional chemotherapy regimens was 17 months compared to 11 months in control (no rHuEPO). Survival was increased by a minimum of 5% in the hematological diagnosis group (myeloma and lymphoma). The authors acknowledge that the interpretive value of the survival data is limited because stages of disease and bone marrow involvement were not controlled in randomization. These results suggest that elevated hgb levels (120 g/L range) prior to undergoing chemotherapy could possibly increase survival by up to six months however a study controlling for all predictive factors would be required to confirm.

Hemoglobin Level as an Indicator of Survival in Total Cancer Population

Additionally, literature confirming hgb level as a prognostic indicator for survival can be found within studies of other tumor groups. Caro et al. (2001) completed a systematic literature review-examining anemia as an independent prognostic factor for survival in cancer patients. This review reports reduced survival times for anemic patients and various malignancies including cancer of the lung, cervix, head and neck, prostate, lymphoma, and multiple myeloma. "In studies reviewed, the median survival was longer for patients without anemia compared with the anemic patient" (Caro, 2001, p. 2216). A diagnosis of anemia could be expected to reduce median survival by 20-43% although the authors state that it is not possible to determine whether anemia is the sole cause of decreased survival or a surrogate for other adverse factors. In summary, improved hgb levels have statistically been correlated with improved survival for the cancer population as a whole and specifically for multiple myeloma patients.

Hemoglobin Level as an Indicator of Survival in Allogeneic Bone Marrow Transplant

So far, hgb level at diagnosis has been shown to be a prognostic indicator for survival through the autologous transplant experience and within other chemotherapy regimes in general. The role of hgb level immediately prior to transplant requires further clarification. Within the allogeneic bone marrow transplant population, survival has been linked to hgb levels immediately prior to transplant. In a retrospective chart analysis (N = 519), Xenocosta et al. (2003) report hgb level less than 110 g/L as a significant, independent risk factor for survival ($p<0.0001$) in multivariate analysis. Survival increased by up to 30% at 180 days post transplant with hgb level greater than 110 g/L. The authors speculate that this influence on survival may reflect direct effects of anemia by mechanisms that may modify hypoxia-inducible genes. The effect of hgb level immediately prior to autologous transplant as an independent prognostic indicator for survival has not yet been explored.

TBI Effectiveness

Speculation regarding the effect of anemia on hypoxia inducible genes further adds to the debate regarding hgb status prior to transplant and the effectiveness of conditioning regimens to provide the best possible chance for cure. Total body irradiation is used, although not consistently, within the chemotherapy regimens prior to allogeneic and autologous bone marrow transplant. Hypoxia within tumour cells is known to impact the effectiveness of radiation. Cells irradiated in the absence of oxygen are more resistant to radiation and conversely oxygenated cells suffer more DNA damage (Bomford & Kunkler, 2003). Increased hgb level has been proven to increase the effectiveness of radiation and therefore improve survival in uterine cervix, head and neck, non-small cell

lung, and prostrate cancer (MacRae, Johnson, & Choy, 2003; Vollmer, Kantoff, Dawson, & Vogelzang; 2002)). Given these findings, it is possible that increased hgb levels immediately prior to transplant may also amplify the effectiveness of radiation therapy in the myeloma population by eradicating tumour cells systemically and within bony plasmacytosis. Increasing the number of patients who achieve a complete response post transplant (little to no evidence of serum/urine monoclonal proteins) enhances longevity and the inability of current treatments to achieve this status in all patients has been the major stumbling block to achieving cure within the myeloma population (see Appendix B). A higher hgb level prior to transplant may increase the effectiveness of conditioning total body irradiation and in so doing prolong survival.

Summary of the Literature

Although there is not a clear quantified definition of anemia presented in the bone marrow transplant literature, it would seem it can be concluded that: 1) anemia affects cancer survival; 2) myeloma patients typically present with anemia and it is prognostic in their survival; 3) myeloma anemia can be corrected; 4) myeloma patients with higher hgb level prior to allogeneic bone marrow transplant have improved outcomes. With respect to myeloma, what is not known is: 1) definitively whether a greater hemoglobin level at transplant correlates with improved survival; 2) whether a higher hgb level immediately prior to transplant presents a survival advantage for autologous bone marrow transplant patients, similar to the advantage for allogeneic bone marrow transplant patients.

Conclusion

Knowledge of the special role that hgb level plays in the experience of an oncology patient is growing. The relationship between superior hgb levels and improved

effectiveness of chemotherapy and radiation has allowed clinicians to predict response to therapy and improve clinical outcomes. Nevertheless, the influence of anemia correction prior to transplant is not well recorded in the literature. As anemia and multiple myeloma are conjoined, studies regarding the relationship between hgb level and survival in this specific patient population are advantageous.

A longitudinal cohort study examining the role that hgb level plays within this population is the focus of this thesis. If hgb level immediately prior to transplant does have a high degree of association with survival, there are potential gains to be explored in future investigations. This thesis examines the relationship between both hgb levels at diagnosis and survival, and length of survival in multiple myeloma patients receiving autologous bone marrow transplant in a single institution (Cross Cancer Institute, Edmonton, Alberta).

Chapter Three

Methods

Design

The purpose of this longitudinal cohort design is to determine the relationship between hgb level at diagnosis and immediately prior to transplant and survival post autologous bone marrow transplant.

Sample

The sample included the charts of individuals who received their cancer care at a large oncology institution serving northern Alberta (Cross Cancer Institute, Edmonton, AB). Inclusion criteria: 1) a diagnosis of multiple myeloma beginning Jan 1, 1995 through to Dec. 31, 2001, and 2) treatment with autologous bone marrow transplant. Exclusion criteria: none. Cases were not excluded due to previous chemotherapy regimens including remote history of prior transplant.

Sample size calculations were based on two main factors: plans to compare the survival curves using log rank analysis, and the realization that regardless of the disease or treatment factor studied, no study had demonstrated more than a small effect on survival. Thus, assuming a small effect size, setting alpha to 0.05, and setting power to 0.80 for two group analysis, the sample size for a one-tailed test was calculated utilizing calculations recommendations by Dupont & Plummer (1998). This work showed that 642 cases per group would be required. As this was outside the possibilities for this institution and this was a preliminary study, a decision was made to recruit all cases from 1995 until 2001.

Based on this analysis, data collection was continued until 50% of cases of MM were deceased. All cases had been diagnosed with multiple myeloma and had received transplant between 1995 and 2001. By including the total population of patients in this time period, findings are the actual population parameters, rather than estimates of these parameters. This approach increases generalizability of the findings and provides a better foundation for calculating sample size estimates for future studies.

Data collection

Cases were identified by the investigator in collaboration with Medical Records personnel at the Cross Cancer Institute. Data were drawn from inpatient records for autologous transplant patients and stem cell product release charts provided to the Cross Cancer Institute by Canadian Blood Services. The following patient and treatment characteristics (including median and range) were included: demographic data (age/gender), disease status at time of transplant (according to Table 2), immunoglobulin isotype, date of diagnosis, hemoglobin at diagnosis (from initial bloodwork performed at CCI or supplied by documentation provided by referring hematologist), hemoglobin prior to transplant (within two weeks prior to autologous bone marrow transplant and prior to blood transfusions), date of transplant, treatment protocols, source of cells (peripheral blood progenitor cells or marrow), volume of cells, number of collections, BMT conditioning regimen, survival status, date and cause of death (see data collection form in Appendix A).

Data Analysis

No assumptions were made about the nature or shape of the distribution. The Kaplan-Meier Product-Limit Estimator was utilized to estimate the survival function

directly from the continuous survival or failure times and log rank testing was used to compare survival curves. Chi square tests were used in the subgroup analysis.

Protection of Human Subjects

The proposal was reviewed by the Ethics Committee of the Cross Cancer Institute and the Health Research Ethics Board, University of Alberta. Written consent from participants whose charts were reviewed was not required. Several strategies were used to protect the anonymity of patients whose charts were reviewed. Data were organized via grouped laboratory variables, diagnostic criteria, and patient characteristics as discussed earlier. This document shows association results as well as a description of the sample by demographic and diagnostic groupings. No identifying characteristics or patient identification numbers have been reported.

Chapter Four

Findings

Sample

A total of 79 patients received an autologous bone marrow transplant from 12 July 1993 to 5 December 2001 for treatment of multiple myeloma. Almost seventy percent of the patients were male. Median age at time of diagnosis was 56 years (range 30 – 70 years). Secretory types diagnosed included IgG (51%), IgA (23%), light chain (20%), non secretory (1%), IgM (1%), IgD (1%), and one remained unknown.

Stage.

Patients at diagnosis and pre-transplant presented with Stage I to III MM with over 64% presenting at Stage III (Durie-Salmon criteria). Five patients were diagnosed with multiple myeloma on the basis of lytic lesions and circulating monoclonal protein but did not have bone marrow involvement greater than 10% of a monoclonal plasma cell. Further, two of these five patients also did not have an elevated monoclonal protein. Incomplete diagnostic information is available for 4 + patients as they were referred from outside physicians after receiving multiple cycles of chemotherapy. The earliest reported serum B_2 microglobulin ranged from 1.36 to 17.41 mg/L and was not routinely measured prior to first dose of chemotherapy. Therefore, results reported here cannot be utilized here to stage MM utilizing the latest international staging system.

Hemoglobin.

At diagnosis, hemoglobin ranged from 68 to 163 g/L (see Table 10). Eighteen percent had severe anemia with hgb < 85 g/L and 38% had a moderate anemia with hgb < 110 g/L. Median hgb was 103 g/L.

Calcium.

A total of 19 patients presented with hypercalcemia (> 2.65 mmol/L) at diagnosis with virtually all resolved prior to transplant (one unresolved). Seventeen patients received pamidronate for their hypercalcemia as well as treatment for lytic lesions. Two remaining patients corrected their serum calcium to within normal parameters through treatment of their myeloma alone (i.e. no pamidronate required).

Lytic Bone Lesions.

The majority of patients had lytic lesions upon diagnosis (67%) and received pamidronate therapy (84%) at some point in the course of their treatment. More than 50% of patients had multiple (i.e. more than 3) lytic lesions upon presentation.

Monoclonal Protein.

Monoclonal serum protein electrophoresis levels ranged from 0 to 89.80 g/L with a median 33 g/L. Thirty four patients had detectable Bence Jones proteins in their urine (median 0.23 g/24 hours). Quantitative immunoglobulin levels (IgA/IgG) were not readily available on all patients and staging has been estimated based on available data.

Creatinine.

A total of twenty five patients were experiencing mild to moderate renal failure with creatinine greater than 125 umol/L and thirteen of these patients would be classified as 'type B' myeloma with creatinine greater than 207 umol/L. (see Table 5 for complete sample characteristic summary).

Table 5

Subject Characteristics (N=79)

	Frequency	%
Gender		
Male	55	69.92
Female	24	30.38
Age		
30-39	1	1.27
40-49	15	18.98
50-59	32	40.51
60-69	28	35.44
70-79	3	3.80
Stage		
1	10	13.33
2	17	22.67
3	48	64.00
Secretory Type		
IgG not specified further	7	8.97
IgG kappa	21	26.92
IgG lambda	12	15.38
IgA not specified further	2	2.56
IgA kappa	13	16.67
IgA lambda	3	3.85

	Frequency	%
light chain not specified	2	2.56
lambda light chain	6	7.69
kappa light chain	8	10.26
non-secretory	1	1.28
IgM kappa	1	1.28
IgD lambda	1	1.28
unknown	1	1.28
Hemoglobin at Diagnosis g/L		
< 85	14	18.42
85 - 110	29	38.16
>110	33	43.52
Calcium		
2.1-2.57	47	66.20
2.58-2.96	12	16.90
2.96	11	15.60
Lytic lesions		
0	25	33.33
1-3	9	12.00
>3	41	54.67
Earliest Serum B_2 microglobulin		
<3.5	38	55.07
3.5-5.4	15	21.74

	Frequency	%
>5.5	16	23.19
Urine SPE g/24 hours		
<4	42	75.00
4-12	11	19.64
>12	3	5.36
Serum SPE g/L		
0-20	24	32.00
21-40	27	36.00
40+	24	32.00

Induction Chemotherapy

Chemotherapy regimens administered at the time of diagnosis include over eight different chemotherapy agents as well as tumor necrosis factor inhibitors. Prior to 1999, patients received a greater variety of initial chemotherapy regimens and repeated cycles of those regimens. Up to 24 different cycles were administered before proceeding to transplant (range 2-24).

A standard of 3 cycles of Vincristine, adriamycine and dexamethasone (VAD) became more prevalent later in 1999. This combination represented the largest majority of chemotherapy regimens administered at 82%. The remaining sixteen patients received single agent or combination chemotherapy including: melphalan and prednisone (MP), interferon, high dose pulse decadron, chlorambucil with vincristine and decadron (CVP). One patient received three different chemotherapy regimens of MP, VAD and

cyclophsphamide/etoposide prior to proceeding to transplant. A second patient also received three different regimens including MP, VAD and interferon alpha. Three patients had previous autologous transplants and data presented pre-transplant reflects the most recent transplant (see Table 6). Patients proceeded to transplant after a median 6.44 months (range 3 – 111 months).

Table 6

Induction chemotherapy

Initial Chemotherapy	Frequency	%
VAD	65	82.28
MP	1	1.27
MP and interferon α	1	1.27
Pulse decadron	3	3.80
CVP	1	1.27
VAD and MP	4	5.06
Prior BMT	2	2.53
VAD, MP, and interferon α	1	1.27
MP, VAD and cyclophosphamide/etoposide	1	1.27

Total # chemotherapy cycles	Frequency	%
2	1	1.32
3	28	66.84

4	21	27.63
5	12	15.79
6	7	9.21
8	1	1.32
9	1	1.32
10	3	3.95
12	1	1.32
24	1	1.32

Stem Cell Mobilization

After induction chemotherapy, patients proceeded to transplant. Transplant autograft was collected from bone marrow alone (3/79), bone marrow and peripheral blood progenitor cells (7/79) and solely from peripheral blood progenitor cells (69/79). Fourteen patients received no mobilizing chemotherapy prior to stem cell collection. The majority (77%) received cyclophosphamide from 2 – 2.5 gm/m2 intravenously. Three patients received cyclophosphamide and etoposide. One patient was mobilized from their last cycle of VAD chemotherapy.

Table 7

Mobilizing/Stem Cell Collection Data

	Frequency	%
Mobilizing chemotherapy		
Cyclophosphamide	61	77.22
Cyclophosphamide & etoposide	3	3.80

	Frequency	%
VAD	1	1.27
None	14	17.72
GCSF		
<5mcg/kg	5	6.58
5.1 – 9.9 mcg/kg	35	46.05
>10 mcg/kg	36	47.37
Days from mobilization to pheresis collection		
9	1	1.36
10	16	27.12
11	24	40.68
12	13	22.03
13	2	3.39
14	3	5.08
Autograft site		
Bone marrow	3	3.80
Peripheral Blood	69	87.34
Bone marrow & peripheral blood	7	8.86
# of stem cell collections		
1	36	46.15
2	16	20.51
3	17	21.79

	Frequency	%
4	7	8.97
5	1	1.28
CD 34 + cells collected (x 10^6/kg)		
0-1.99	11	14.86
2-3.9	6	8.11
4-5.9	13	17.57
6-7.9	10	16.22
8-9.9	8	10.81
>10	24	32.43

Granulocyte colony stimulating factor was administered to all but 3 patients to aid in mobilization of stem cells for collection. The range of dose administered was 4.29 mcg/kg up to 11.64 mcg/kg with patients receiving 10 mcg/kg most often (20/76). Fourteen patients received stem cell factor 20 u/kg in addition to GCSF for stem cell mobilization. Most frequently, a single pheresis collection was required to collect enough stem cells for transplant (46%). However, up to six pheresis collections were required in a single patient without collecting > 2 x 10^6/kg CD34 cells and this patient went on to have a bone marrow harvest to supplement their pheresis collection. Of note, this patient did not receive mobilizing chemotherapy and GCSF was at 5 mcg/kg which is on the lower end of range. The time from mobilizing chemotherapy to stem cell collection ranged from 9 to 14 days (median 11 days) with a median CD34+ stem cell collection of 6.74 x 10^6/kg (see Table 7).

Autologous Transplant

Time from diagnosis to transplant ranged from 93 to 3395 days with time to transplant decreasing after 1997. Melphalan 180 – 200 mg/m^2 was uniformly administered as consolidation chemotherapy. Granulocyte colony stimulating factor (GCSF) ranging from 4.49 mcg/kg to 7.56 mcg/kg was administered to aide in engraftment to all but three patients who received none.

Total CD34+ cells infused ranged from 1.02 to 70.40 x 10^6/kg. Upon administration of the autograft, 6 patients experienced facial flushing, 3 experienced throat tightness, 2 experienced nausea and 2 had abdominal cramps. One patient lost consciousness briefly. In all, 14% of patients experienced an infusion reaction of some type. Time to neutrophil engraftment (ANC > 0.5 or total WBC > 1.0 x 10^9) ranged from 9 to 31 days with a median 11 days (see Table 8). Time to platelet engraftment (platelet > 50 x 10^9) ranged from 11 to 188 days with a median of 15 days.

Length of hospital admission ranged from 4 to 79 days with a median of 16 days. Five patients were re-admitted with post-transplant complications within several days of discharge and had an additional length of stay from 3 to 37 days. Complications experienced by patients during their transplant admission include: stomatitis, weight loss with need for total parenteral nutrition, febrile neutropenia, diarrhea, nausea, acute renal failure, oral/esophageal candidiasis, congestive heart failure, acute cholecystitis, gastrointestinal bleeding, atrial fibrillation, pneumonia, pulmonary edema, UTI, ICU admission, urinary retention, folliculitis, hypoxia, hypokalemia, leg pain, and hypertension.

Table 8

Days to Engraftment and Length of Stay

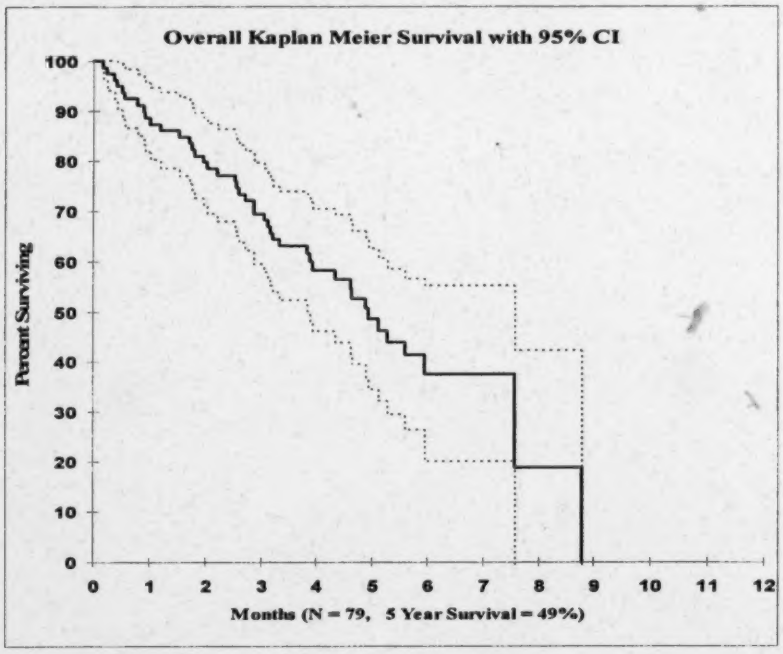
	Frequency	%
Neutrophil engraftment		
9	1	1.28
10	22	28.21
11	21	26.92
12	18	23.08
13	6	7.69
14	1	1.28
15	3	3.85
16	1	1.28
>16	5	6.41
Platelet engraftment		
11-12	14	21.87
13-14	12	18.76
15-16	13	20.31
17-18	9	14.07
19-20	6	9.38
21-22	3	4.69
>23	7	10.94
Length of hospital stay		

	Frequency	%
Length of hospital stay		
<10	8	10.13
11-15	30	37.97
16-20	23	29.12
21-25	11	13.92
>25	6	8.86

Overall Survival From Time of Transplant

Out of 79 reviewed patients from 1995 to 2001, 36 (45%) remain alive at time of reporting (see Figure 1). Measured from time of transplant, overall survival at 5 years is 49% (95% confidence interval 35 – 64%).

Overall Kaplan Meier Survival Curve from Time of Transplant



Patients referred for autologous transplant also experienced a myriad of co-morbidities either before or after the transplant which may have impacted their length of survival (see Table 9). Cause of death (as listed on their death certificate) was most often listed as from the multiple myeloma itself at 72% of cases. Patients also expired from congestive heart failure, coronary artery disease, respiratory failure, rupture of aortic aneurysm, and acute renal failure.

Table 9

Co-morbidities and Cause of Death

	Frequency
Cause of Death	
MM	31
CHF	2
CAD	1
Respiratory failure	3
Ruptured Aortic Aneurysm	1
Acute renal failure	1
Co-morbidities	
Type 2 Diabetes	5
Coronary artery disease	3
Basal Cell carcinoma	2
Prostate cancer	2
Chronic renal failure	2

	Frequency
Hypertension	2
History of pulmonary hemorrhage	1
Beta Thallassemia	1
Atrial fibrillation	1
Hypothyroidism	1
Pancreatitis	1
Von Willebrands	1
COPD	1

Hemoglobin at Transplant

Prior to transplant, hemoglobin ranged from 73 to 141 g/L (median 106 g/L) with less than 4% severely anemic with hgb < 85 g/L (see Table 10). Fifty four percent experienced moderate anemia with hgb < 110 g/L.

Table 10

Hemoglobin at Transplant

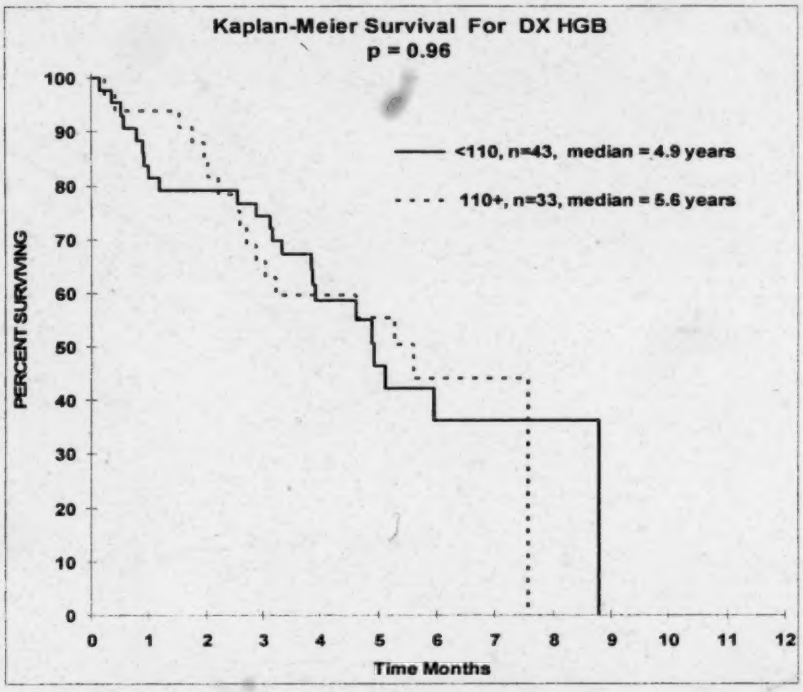
	Frequency	%
Hemoglobin at Transplant		
< 85	3	3.80
85 - 110	44	54.43
>110	33	41.77

Research Question 1: The Relationship Between Hemoglobin at Diagnosis and Survival

Median overall survival measured from time of transplant for patients with a hemoglobin less than 110 g/L at diagnosis (n= 43), was 4.9 years (1800 days, 95% confidence interval 1403 – 3212) using product limit survival estimates. For those patients with a hemoglobin greater than or equal to 110 g/L (n=33), median overall survival was 5.6 years (2045 days, 95% confidence interval 1047 – 2765). The difference in these two curves was not significant (p = .95). The hazard ratio for hgb level greater or equal to 11 versus less than 110 g/L is 0.984 (95% confidence interval 0.522 – 1.856).See Figure 2.

Figure 2

Kaplan Meier Survival Curves from Transplant for Hemoglobin at Diagnosis



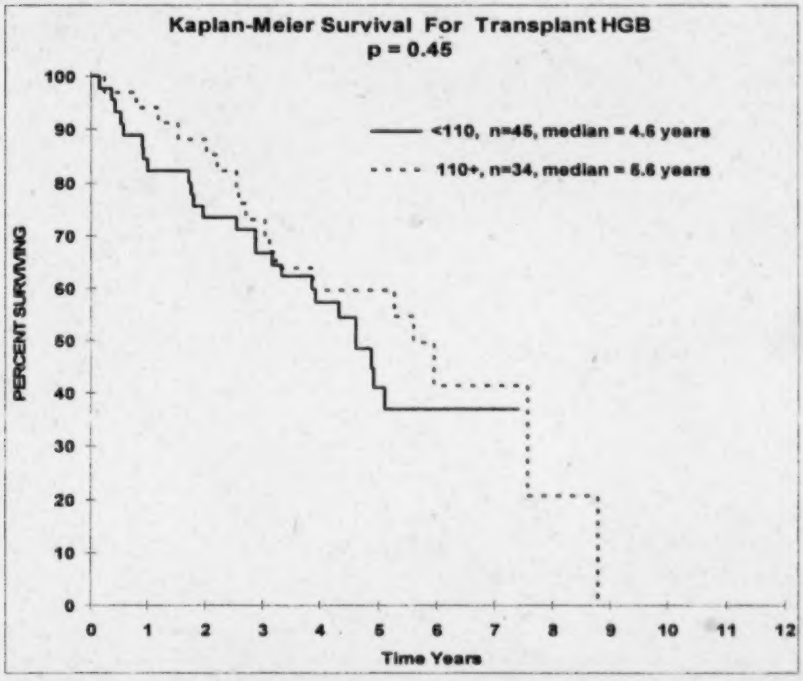
By Cox regression analysis, hemoglobin less than or greater than 130 110 or 90 g/L was not predictive for survival after transplant (p=.63, .96, and .57 respectively).

Research question 2: Hemoglobin Pre-transplant and Survival

Patients with hemoglobin level less than 110 g/L (n= 45) at time of transplant had a median survival of 4.6 years (95% confidence interval 3.3 - 7.4+ years as upper limit not reached) utilizing product-limit survival estimates for analysis. Participants with hemoglobin level greater than or equal to 110 g/L (n= 34) at transplant, survived 5.6 years after transplant (9.5% confidence interval 3.2 - 8.8 years) The difference in these two survival curves was not significant (p=.45). Hazard ratio for hemoglobin greater than or equal to 110 g/L versus < 110 g/L was 0.776 (95% confidence interval 0.413 – 1.459) (see Figure 3).

Figure 3

Kaplan Meier Survival Curve from Transplant for Pre-transplant Hemoglobin



Again, to ensure hemoglobin parameters beyond the 110 g/L target range were not limiting the scope of analysis, the parameters were changed to less than or greater

than 90 g/L and 130 g/L. Using Cox regression, there was no predictive value for these parameters (p=.87 and .51 respectively).

Pre-transplant Hemoglobin Sub-group Analysis

Data were further analyzed after being divided into the two groups of hgb level less than or greater than or equal to 110 g/L prior to transplant (see Table 11). The groups were similar in age at diagnosis, stage at diagnosis, total CD34+ cells collected during apheresis, and number of apheresis collections required meeting the 2×10^6/kg target. Length of stay was different between groups with lower hemoglobin having 17 days in hospital and higher hemoglobin having 14.5 days in hospital. This was a significant difference (p=.0044). Also significantly different was the time to platelet recovery with the higher hemoglobin recovering 3.5 days faster (p+.00533). There was also a trend toward significance in neutrophil recovery for the higher hemoglobin group (11 days versus 12 days, p=.0644). It was not possible to compare staging immediately prior to transplant between the two groups as diagnostic testing required for staging (including a repeat bone marrow biopsy and skeletal survey) was not routinely performed on the majority of patients.

Table 11

Hemoglobin prior to Transplant Subgroup Analysis

	Median		p value
	< 110 g/L	> 110g/L	
Age at diagnosis	59	56	.0874
Stage at diagnosis	3	3	.9875
Pheresis	6.5	7.4	.4826

	Median		p value
	< 110 g/L	> 110g/L	
# of days to mobilization	11	11	.3035
# of collections	2	2	.9273
Length of stay	17	14.5	.0044
Neutrophil recovery	12	11	.0644
Platelet recovery	17	13.5	.00533

Chapter Five

Discussion of Findings

Sample

In comparing this sample to the literature, there are similarities and a few differences. The median age of this group is lower at 56 years than expected as the literature had stated 70 years is the median at diagnosis (Zaidi & Vesole, 2001). However, at 56 years, this is very reflective of the many studies examining the use of autologous transplant (see Appendix B). It is possible that those patients diagnosed with multiple myeloma with a greater age were not referred for transplant and this has lowered our median. As expected, only a few patients are under 40 years of age (1.27%) and men also outnumber women (55:24). The immunoglobulin subtype frequencies are also as expected with IgG at 51% (55% expected), IgA 26% (23% expected), light chain at 20% (14% expected), and non-secretory and IgD being rare at 1% as expected (Malpas, 1998; Harousseau, 2002).

Anemia

Fifty six percent of patients were found to have anemia upon diagnosis within this population. Up to 18% had severe anemia with hgb < 85 g/L. These results fall within expected parameters from previous studies (Meharchand, 1998). For 14% of patients, severe anemia had been improved through myeloma chemotherapy treatment but they still remained moderately anemic. In the course of treatment, 52% of patients experienced a rise in their hemoglobin. This rise was as much as 53 g/L. In contrast, for 43% of patients, hemoglobin levels declined within a range of -20 g/L to -55 g/L. Five percent of

patients' hgb levels remained unchanged from the time of diagnosis. The median overall change in hgb level was a loss of 30 g/L.

Interestingly, hemoglobin levels did not increase through the course of induction chemotherapy. Immediately prior to transplant, slightly more than half the patients experienced a decrease in their hemoglobin level from their diagnosis level. This is an unexpected finding as it was theorized that hemoglobin would increase through the course of therapy with decreased tumor burden. It is speculated the myelosuppressive effects of chemotherapy outweigh the decreased tumor burden within the marrow. Of note, mobilization chemotherapy was administered as little as three weeks prior to admission for autologous transplant. This may not be sufficient time to allow for full marrow recovery and improved hemoglobin levels although sufficient to proceed with transplant. Further observations into hemoglobin trends between mobilization chemotherapy and admission for myeloablative therapy may be prudent. Phlebotomy induced blood loss may have also contributed to lowered hemoglobin levels.

Correction of Anemia

Ten patients received transfusions of packed red cells upon initial diagnosis. One patient was found to have a folate and vitamin B12 deficiency which was corrected. Another patient received recombinant erythropoietin 10,000 units three times weekly at time of diagnosis due to religious constraints regarding transfusions of blood and blood products. Erythropoietin was continued throughout initial chemotherapy and transplant admission. This patient's initial hemoglobin was 85 g/L and there was a 31 g/L increase in serum hemoglobin to a level of 116 g/L prior to transplant. This patient did not require blood transfusions prior to or during the transplant experience although monitoring of

bloodwork was not as extensive in the immediate post transplant period as it was with other patients who may have masked transfusion need. This patient is alive 4.2 years following bone marrow transplant.

Administering erythropoietin to subvert transfusion needs when a patient has religious restrictions has been successfully described by Ballen et al (2000) in a single case study. Henry (1997) also describes a small study administering erythropoietin for 7 days prior to transplant in a small group of patients (N=16). Transfusion requirements were reduced but there is no survival statistics reported.

Hemoglobin and Survival

This study did not find any association between hemoglobin level at diagnosis nor hemoglobin level prior to transplant (overall) and survival. Both Gertz (1999) and Child (2003) found hemoglobin level at time of initial diagnosis to be predictive of survival for patients with multiple myeloma receiving autologous bone marrow transplant. Their studies were prospective (one being randomized) involving larger groups of patients than this sample (Gertz N = 118,. Child N = 407). Unlike these trials, hemoglobin at diagnosis was not found to be predictive for survival within this population of 79 patients. This does correspond with Palumbo's (1999) matched pair analysis which also did not find any relationship between survival and hemoglobin level at diagnosis.

Dividing the patients into subgroups with hgb < 110 g/L or >= 110 g/L immediately prior to transplant, this study also did not find any significant difference in survival. This is in contrast to Xenocosta's (2003) study of hemoglobin levels and survival within the allogeneic patient population. Survival in this study was measured at 180 days as this is the treatment period related to the greatest mortality whereas our study

has follow-up to 13 years for patients diagnosed in the late 1980's. It would be interesting to note if the survival curves in Xenocosta's study continue to remain separated further out into the future.

The lack of correlation between hemoglobin level and survival may be hindered by the power of the study. Admittedly, this study is underpowered at .1150. A total of 1284 cases (642 each group) would be required to establish alpha at 0.05 and power of .80. To accomplish this, a large multicenter study would need to be completed. Alternatively, if follow up were to be completed for a total of 15 years, the study would be adequately powered with the same number of total cases. Follow-up analysis on the 79 cases presented is planned.

There are also many factors now known to be predictive of survival that are unknown within the total and subgroup population(s). Serum β_2 at diagnosis along with albumin levels according to the new International Staging may reveal that there are a disproportionate number of patients of higher/lower stage between groups. Additionally, cytogenetic testing was just beginning to be studied during the time frame of this chart review. Three patients were known to have a measurable 11q deletion however quantification and significance of the results had not yet been validated. Patients also went on to receive a variety of maintenance or salvage chemotherapy regimens that may have impacted survival and skewed comparisons. Co-morbidities were also not controlled between the cohort groups and may have unduly impacted length of survival.

Length of Stay

An unexpected finding upon subgroup analysis included a 2.5 day decrease in length of stay for patients with higher hemoglobin levels. Median length of hospital

admission for autologous BMT is reported from 18 to 20 days with range extending from 12 – 75 days (Magagnoli et al., 2003, Prieto et al., 2002) which is similar to our population at a median of 16 days (range 4 to 79 days). Factors influencing length of stay have been found to include engraftment delays, psychiatric morbidity, gastrointestinal complications and infections (Cetkovsky, Skopek & Schutsova, 2000; Prieto et al). Klaesson et al. (1994) administered rHuEPO immediately *post* allogeneic transplant with a target hemoglobin greater than or equal to 110 g/L. These patients were found to have a two day shorter length of hospital admission at a $2000 (U.S) savings per patient as well as decreased need for packed red cell transfusion. A recently reported study by Martine (2005) has examined the use of erythropoietin prior to autologous transplant. It is impossible to compare length of hospital admission with this study to our sample as this research center conducts its autologous transplants entirely as an outpatient experience.

Platelet and Neutrophil Engraftment

An unexpected finding upon subgroup analysis was that patients with higher hemoglobin had decreased time to platelet engraftment (p=.005) and a trend towards lower time to neutrophil recovery (p=.60). More rapid engraftment has also been seen as a trend in other studies examining the use of erythropoietin post transplant (Chao, 1994; Link et al., 1994) although it did not reach statistical significance in these studies.

It may be that patients with greater hemoglobin levels have superior levels of circulating endogenous erythropoietin. Autologous BMT for treatment of solid tumors have found improved engraftment in myeloid and platelet lineages when treated with exogenous rHuEPO (Ayash, et al., 1994). A recent trial administered erythropoietin to 22 MM patients immediately after mobilization and prior to transplant chemotherapy and

found reduced red cell and platelet transfusion requirements in comparison to historical controls ((Martino et al, 2005). Other studies have not shown a benefit with erythropoietin administered *post* conditioning therapy in autologous transplant to improve engraftment and reduce transfusion requirements although none of these studies include multiple myeloma within the sample (Vannucchi, A., et al, 1996; Chao, 1994; Link, 1994).

Implications for Practice and Research

Multiple myeloma patients with a higher hemoglobin level at diagnosis and prior to autologous bone marrow transplant did not experience improved survival. Since steps are being put in place to continue to use the database developed in this study to monitor the 79 patients in this study as well as new patients, future follow up of the effect of hemoglobin level on survival with a larger sample will eventually be possible. These plans raise the issue of a minimum dataset that would permit the ongoing study of health outcomes and quality of life in this population. The following list of variables are recommended for inclusion, given studies or clinical experience which have linked them to survival and/or quality of life: age, sex, secretory type, hemoglobin at diagnosis, stage (β_2 microglobulin levels and albumin), creatinine, cytogenetic testing results, pamidronate therapy, initial chemotherapy for induction, number of cycles given, use of erythropoietin, source of stem cells, mobilizing chemotherapy, date of mobilizing chemotherapy administration, use of granulocyte colony stimulating factors for mobilization and post conditioning, date of stem cell collection, number of cells collected, conditioning therapy, date conditioning therapy administered, date of autograft

infusion, date of neutrophils/platelet engraftment, admission/discharge date, status (alive/dead) and date status reviewed.

The findings of this study suggest that nurses who monitor patients with multiple myeloma should explore ways, such as the administration of exogenous erythropoietin, to maintain patients' hemoglobin levels above 110 g/L. Although a hemoglobin level greater than 110 g/L was not associated with increased survival, improvements in length of hospital admission, time to platelet recovery, and a trend toward improvement in myeloid engraftment were found. This is an important finding because, in addition to the costs savings associated with decreased length of stay, additional potential benefits of include reduced exposure to allogeneic transfusion and the risks associated with this intervention, and possible reduction in risks of infection due to earlier engraftment.

Improved hemoglobin is also known to improve quality of life for cancer patients. Since curative treatments for multiple myeloma are not yet available, interventions that improve quality of life are important. When this benefit is considered together with the health outcomes outlined above, the significant opportunity to reduce costs to the health care system by increasing hemoglobin level pre-transplant clearly warrants further investigations. A prospective trial examining patient stage, hemoglobin at diagnosis, hemoglobin prior to transplant, stage, chemotherapy treatment, engraftment of neutrophils/platelets, length of stay, and quality of life before, throughout, and after the transplant experience is recommended.

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Appendix A

Data Collection Worksheet

E#	Initials:	Sex: M F	DOB	
Date Dx		Secretory Type		
HbG dx	Dx Ca:	SPE monoclonal g/L:		
Dx lytic lesions		Beta2 microglobulin:		
Dx creatinine		BM % plasma cells:		
Urinary kappa/lambda 24 hours		Dx Stage		
Initial chemotherapy				
Eprex preBMT		Pamidronate	Y/N	Date
Mobilizing chemotherapy				
PBSCT or BM				
GCSF mobilizing Y N	dose/frequency	Wt	Date	
CD34 cells collected		Date collected:		
Hgb PT		Ca PT		

Lytic PT		PT Monoclonal immunoglobulin SPE:	
PT creatinine			
Admission date			
Condition chemo date			
Conditioning chemo			
GCSF post conditioning		Wt	Dates
# CD34 cells infused		Dates	
ANC engraftment			
Platelet engraftment			
PRBC transfusion dates			
Platelet infusion dates			
BMT Complications			
Discharge date			
LOS	To be calculated		
Status: Alive or Dead		Date	
Cause			
Length survival	To be calculated		
Comorbidities:			

Comments:

Appendix B

Table B1

Review of Autologous BMT MM Trials

Author	Year	Age	Target population	Method	Result	ANC	PLT
Barlogie	1986	63	N = 23 Refractory or not ever responding	M 80 with no stem cell rescue or M 140 followed by stem cell rescue.	OS 4 mos no BMT vs 14+ months with BMT; 50% RR with BMT vs 20% RR VAD		
Barlogie	1987	50	N = 7 Resistant to VAD BMT up to 4- 106 months from dx	TBI 850cGy + M 140 plus BMT	OS 9 mos; From 6-30% grafts contaminated with tumor cells as collected while refractory	19-62	20 – 99
Fermand	1989	41	N= 8 Relapsed – from 5 to 48 months from dx to BMT	C/A/V/P to mobilize circulating stem cells. CAV x 3 to 4 mos. Condition: Carmustine, E/M 140 + TBI 10 Gy then BMT	OS Median 13 months. Determine 2 x 10^6/kg nucleated cells safe minimum graft	16	34
Jagannath	1992	50	N = 75 Relapsed MM from 3-79 months from dx to BMT	Mobilize: C + GCSF. Condition: M 200 and GCSF post	85% at 1 year, 68% response rate. Better survival if less than 1 year from dx	15 days with GCSF support	16
Attal	1992	45	N= 35 Untreated stage 3; up to 8.7 months from dx to BMT	Induction: VAD or VMCP until monoclonal protein plateau, stem cell collection. Condition: M 140 + TBI 8 Gy. IFN maintenance.	81% survival at 41 month; CR predictive for survival	17	19
Harousseau	1992	51	N= 97 2 groups 1)Untreated and 2) relapsed/refractory BMT from 2 – 45 months from dx	M 100-140, marrow/PBSC collection, Conditioning with M 140 or M 140+cyclo+TBI or Busulfan/cyclo	Untreated MM 28%CR vs 20% in relapsed, Overall survival 24 months	24.5	18.5

C = cyclophosphamide; M = Melphalan mg/m^2; TBI = total body irradiation; A = adriamycin; V = vincristine; D = dexamethasone; B= busulfan; E = etoposide; P= prednisone; GCSF = granulocyte colony stimulating factor; IFN = interferon; thal = thalidomide, dx = diagnosis; OS = overall survival; RR = response rate; CR = complete response, HR=hazard ratio

Author	Year	Age	Target population	Method	Result	ANC	PLT
Fermand	1993	44	N= 63 Previously treated stage 2-3 refractory or relapsed with BMT 3 – 90 months from dx	Stem cell collection immediately or following CVAP. Consolidation with carmustine/E/M/C TBI with IFN maintenance	OS 59 months; survival improved with < 6 courses prior chemotherapy	15	16
Dimopoulos	1993	49	N= 40 Primary resistant or relapsed MM with purged marrow using antiCD19 monoclonal antibodies	Marrow or PBSC purged, Conditioning Thiotepa/B/C + GCSF post. IFN and decadron maintenance.	OS not reported; better hematologic recovery with PBSC	9 BM; 15 PBSC	41 BM; 15 PBSC
Vesole	1994		N= 135 Resistant and relapsed MM 78%>12 mos from dx to BMT	**Retrospective analysis.** Mobilize: C and GCSF. Condition: M 100 vs M 140 or thiotepa and TBI 850cGy with BMT or M 200 and BMT with 2nd BMT planned (allogeneic or autologous) if no CR. IFN maintenance	CR 24% with first BMT up to 43% post 2nd BMT. OS 7 mos M 100; 7 mos M 140; OS 43 mos M 200 +- 2nd BMT..		
Schiller	1995	51	N= 37 Chemo responsive or stable stage 1 - 3. No refractory or relapsed patients. From 4 – 47 months up to BMT.	C/P + GCSF to mobilize. Apheresis. Conditioning: B/S. GCSF post. IFN and decadron maintenance.	1 yr OS 68%; prolonged hematologic recovery if graft < 2 x 10^6 CD34/kg	12	>20 = 12 days
Marit	1996	54	N= 73 Stage 1 – 3 previously treated. From 4 – 180 months dx to BMT.	Mobilize: C+ GCSF Condition: M 140 +TBI 8 – 15 Gy.	3 yr OS 77%; Improved engraftment with higher CD34 graft.	10.5	12
Bensinger	1996	51	N= 63 Stage 1 -3 previously treated. From 0.4 – 8.4 years to BMT	Mobilize: C/E/Cisplatinum + GCSF. Conditioning: B/C +TBI or B/M/thiotepa. IFN maintenance	OS at 3 years 43%	PBSC – 10 BM – 15 Mix - 9	>20 PBSC – 10 BM -27 Mix – 8

C = cyclophosphamide; M = Melphalan mg/m^2; TBI = total body irradiation; A = adriamycin; V = vincristine; D = dexamethasone; B= busulfan; E = etoposide; P= prednisone; GCSF = granulocyte colony stimulating factor; IFN = interferon; thal = thalidomide, dx = diagnosis; OS = overall survival; RR = response rate; CR = complete response, HR=hazard ratio

Author	Year	Age	Target population	Method	Result	ANC	PLT
Attal	1996	57	N= 200 Untreated stage 2 – 3. Time from dx to BMT 4 – 11 months.	RCT VMCP alternate q3 weeks with BVAP x 12 months (18 cycles) IFN maintenance Versus VCMP alternate BVAP x 6 with conditioning melphalan 140+TBI 8 Gy. IFN maintenance.	Control = median OS 37.4. Probable 5yr OS 12% BMT = 5 yr OS not reached, estimated 52%. IFN effect marginal.	18	22
Bjorkstrand	1996	46	N= 189 Retrospective case analysis stage 1 – 3. Median time to BMT 15 mos.	Allogeneic: TBI + C vs TBI + C/M vs TBI +C/M + other vs B/C Autologous: TBI+M vs TBI + other	Allo Median OS 18 mos TRM 41% Auto median OS 34 mos TRM 13%		
Barlogie	1997 2003 f/u data	51	N= 231 MM untreated or only 1 cycle standard chemotherapy. 7.5 mos from dx to BMT. 13 mos 2nd BMT.	**Case controlled analysis** VAD induction. Cyclo + GCSF mobilizing. EDAP, then to M 140 + TBI or M 200 for second BMT if not good PR. IFN maintenance.	Median survival 68 months; TRM 3% VAD, 1% auto BMT, 2% 2nd BMT.		
Fermand	1998	47.5	N= 202 Untreated MM for stage 2 – 3.	**RCT** Mobilization CHOP + GCSF, randomized to VAMP x 3 or 4 cycles then M/lomustine TBI vs VMCP until plateau then relapse and treat with VAMP and M/lomustine/TBI. IFN maintenance.	OS 64 months for both late and early BMT. Relative risk late BMT 1.02.		
Alegre	1998	52	N=259 Untreated Stage 1-3 MM	**Retrospective review.** Numerous chemotherapy inductions, C +- GCSF or GCSF alone to mobilize, to M +- TBI/B or C/TBI.	OS 35 months; # of chemotherapy regimens most prognostic and disease resistance at time of transplant	12	18 (5 patients not reached > 50)

C = cyclophosphamide; M = Melphalan mg/m^2; TBI = total body irradiation; A = adriamycin; V = vincristine; D = dexamethasone; B= busulfan; E = etoposide; P= prednisone; GCSF = granulocyte colony stimulating factor; IFN = interferon; thal = thalidomide, dx = diagnosis; OS = overall survival; RR = response rate; CR = complete response, HR=hazard ratio

Author	Year	Age	Target population	Method	Result	ANC	PLT
Vescio	1999	51.5	N= 131 Stage 2 – 3 with up to 3 cycles previous chemotherapy but no disease progression.	**RCT mutlicenter.** Mobilize: C/P + GCSF with/without CD34 selection. On to B/C and GMCSF post.	CD 34 selection no benefit to engraftment. OS not reported (1 yr data).	12	11 CD34 selected vs 9 for CD 34 not selected
Palumbo	1999	64	N= 71 Stage 2 -3 with poor performance status and elderly.	**Matched pair analysis** C/M q2mos x 3 vs MP x 6 followed by VAD x 3 then C to mobilize and M100 q2 months x 2 with GCSF support for BMT	OS MP oral – 48 months vs not reached in BMT 56+ months.	Only < 0.5 x 3 days d/t less dose M	Not < 70 through program
Rajkumar	1999	53	N= 75 Primary refractory or relapsed stage 2 – 3. 5 - 88 months from dx to BMT.	VAD as induction followed by M + TBI 12 Gy or M alone or M/C or other	OS 53 months from dx, from BMT 18 mos.		
Gertz	1999	52	N= 118 Primary failure or relapsed on or off therapy. Median time dx to BMT not reported.	VAD x 4 as induction. Mobilize: C +- GCSF or no mobilization. Consolidation: M 200 or M 140+TBI 12 Gy. If no response to BMT direct to transplant. If response BVMCP x 12 and BMT at first sign relapse.	Survival from BMT 17.2 mos. Overall survival all pts 58.5 mos. No deleterious effect late transplant.		
Vesole	1999	55	N= 56 Primary refractory MM	**Multi-institutional trial.** Mobilize: C+ GMCSF. Conditioning: M 100 x 2. IFN maintenance	OS 19 months from transplant		
Facon	1999		N= 102 Untreated MM all stages.	Mobilize: Stem cell factor with C + GCSF to improve engraftment	No difference in time to engraftment despite higher CD34 count.		
Siegel	1999	52 and 67	N= 550 Matched pair analysis for use of auto BMT in elderly		TRM 2% younger, 8% older. No difference in engraftment or survival data.		

C = cyclophosphamide; M = Melphalan mg/m^2; TBI = total body irradiation; A = adriamycin; V = vincristine; D = dexamethasone; B= busulfan; E = etoposide; P= prednisone; GCSF = granulocyte colony stimulating factor; IFN = interferon; thal = thalidomide, dx = diagnosis; OS = overall survival; RR = response rate; CR = complete response, HR=hazard ratio

Author	Year	Age	Target population	Method	Result	ANC	PLT
Sirohi	2000	67 vs 55	N=34 Stage 1 – 3. Time from dx to BMT 14 mos.	**Matched Pair Combination** Multiple chemotherapy induction on to consolidation M or B.	TRM 17.6% elderly to 11.7% for matched pair. Not statistically significant. OS elderly 3.59 vs 3.01 yrs.	20 elderly 17	24 elderly 35
Lemoli	2000	51.5	N= 82 Stage 1 – 3 time from dx to BMT 15 mos.	VAD or other. Mobilize C + GCSF. Conditioning: M 200 or M 140 + TBI. Some on to 2nd transplant.	3 yr OS single BMT 76% vs 92% for 2nd BMT.	11	15
Lenhoff	2000	52	N= 548 Stage 1 – 3. From dx to BMT 5 mos.	**Multicenter case control matched groups** Induction: VAD x 3. Mobilize: C + GCSF. Consolidation: M 200. IFN maintenance. Compared to matched controls no BMT.	TRM 1.4% BMT. OS control 4 mos vs not reached in BMT (54+ mos)		
Blade	2000	54	N= 64 Retrospective analysis of newly diagnosed MM stage 1-3	Alternating VCMP/VBAP compared to induction of same regimens x 3 or 4 cycles consolidate M 140 + TBI 12 Gy or M 200 and C/E/carmustine and tandem transplant	No difference overall survival.		
Martinelli	2000	38	N= 229 Patients achieving CR after allo/auto single/double BMT	Molecular analysis for residual disease using PCR for IgH gene	MCR 50% for allogeneic vs 16% for autologous. Relapse rate 41% for those not achieving MCR vs 16% for those who do.		

C = cyclophosphamide; M = Melphalan mg/m^2; TBI = total body irradiation; A = adriamycin; V = vincristine; D = dexamethasone; B= busulfan; E = etoposide; P= prednisone; GCSF = granulocyte colony stimulating factor; IFN = interferon; thal = thalidomide, dx = diagnosis; OS = overall survival; RR = response rate; CR = complete response, HR=hazard ratio

Author	Year	Age	Target population	Method	Result	ANC	PLT
Michallet	2000	55	N= 31 Stage 2 -3 receiving 3 -6 cycles of VAD and achieving at least PR	Mobilize: C + GMCSF. M 140+TBI. Re-infusion of CD34 and Thy1 selected cells.	Higher bacteremia 26 % and febrile neutropenia 91% and viral infections.	11	28
Desikan Tricot	2000 2002	53	N= 515 N= 100 Follow up to Barlogie 1997/2003	Same as Barlogie.	TRM 2.7% first BM vs 4.8% second BMT. Chromosome 13 deletion separate diagnostic entity for response.		
Dyson	2000	51	N= 34 Untreated MM or <2 chemotherapy regimens and advanced disease	Induction: VAD x 3. Mobilization: C + GMCSF. Consolidation: C/E and first BMT with CD 34 selected cells followed by GMCSF and second harvest with B/M 140 and 2nd BMT. IFN maintenance	See Horvath 2004.		
Olivieri	2001	63	N= 48 Elderly and receiving autologous BMT for hematologic disorder (16 MM)	Mobilizing: CF or C/DHAP or C/E or GCSF. Consolidation: M or B/C.	TRM 1.8%, 67% febrile. OS 36 months. Best hem recovery with CD 34 5 x 10^6/kg – 7.8.	11	17
Badros	2001	72	N= 70 Newly diagnosed and refractory MM	C and GCSF to mobilize. Consolidation: M 200 first BMT and M 140 with 2nd BMT + GCSF.	2% TRM. 3 year Median OS 24 mos.	11	
Stewart	2001	21	N= 190 Stage 2 or 3 stable or responsive disease. Up to 2 years from dx to BMT.	**Multicenter randomized trial** Mobilize C/P + GCSF. Randomized to CD 34 selection vs no selection. Consolidation: B/C + GMCSF post.	No difference in ANC/platelet recovery. OS median 50 mos in selected and not reached in unselected arm.	12	12

C = cyclophosphamide; M = Melphalan mg/m^2; TBI = total body irradiation; A = adriamycin; V = vincristine; D = dexamethasone; B= busulfan; E = etoposide; P= prednisone; GCSF = granulocyte colony stimulating factor; IFN = interferon; thal = thalidomide, dx = diagnosis; OS = overall survival; RR = response rate; CR = complete response, HR=hazard ratio

Author	Year	Age	Target population	Method	Result	ANC	PLT
Singhal	2002	54	N= 222 Untreated or < 2 cycles previous chemo for all stages	CVAMP q3 weeks until maximal response (median 5 cycles). GCSF to mobilize. Consolidation: M 200. IFN maintenance.	Lack of response to induction chemo is not predictive for survival. Do not disqualify for BMT if primary refractory.		
Moreau (1)	2002	60.5	N= 282 Previously untreated stage 2 or 3 with no tumor progression on VAD	**Multicenter RCT trial.** Induction: VAD x 3. Mobilization: C+ GCSF +/- stem cell factor or GCSF alone. Consolidation: randomized to M 140 + TBI 8 Gy or M 200. IFN maintenance.	VAD CR 8% Mel200 – CR 35%, probability of survival at 45 mos 65.8%. Mel140 – 29% CR, median OS 43 mos. No benefit to TBI in consolidation	10	7
Moreau (2)	2002	55	N= 127 Stage 1 -3 untreated	VAD, MP or alternating VMCP/VBAP. Consolidation: M 200 vs M 150+TBI and 2nd BMT for 63% of pts. 3rd BMT for further relapse.	OS @ 12 years 24.9%. Median OS 49 mos. 4 patients alive and disease free @ 12 years of 3 of them are allo transplants..		
Child	2003	55	N= 407 Previously untreated MM	**RCT**. Doxorubicin, carmustine, C+M q6weeks until maximum response versus Same chemo until maximum response then mobilize: C + GCSF. Conditioning: M 200 or M 250+TBI. IFN maintenance.	Chemo alone – OS 42.3mos BMT OS 54.1 months		

Note. 1) Moreau, P., Misbahi, R., Milpied, N., Morineau, N., Mahe, B., Vigier, M., et al. (2002). Long term results (12 years) of high dose therapy in 127 patients with de novo multiple myeloma. *Leukemia, 16*, 1839-1843.
2) Moreau, P., Facon, T., Attal, M., Hulin, C., Michallet, M., Maloisel, F., et al. (2002). Comparison of 200 mg/m2 melphalan and 8 Gy total body irradiation plus 140 mg/m2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. *Blood, 99*(3), 731-735.

C = cyclophosphamide; M = Melphalan mg/m^2; TBI = total body irradiation; A = adriamycin; V = vincristine; D = dexamethasone; B= busulfan; E = etoposide; P= prednisone; GCSF = granulocyte colony stimulating factor; IFN = interferon; thal = thalidomide, dx = diagnosis; OS = overall survival; RR = response rate; CR = complete response, HR=hazard ratio

Author	Year	Age	Target population	Method	Result	ANC	PLT
Magagnoli	2003	65	N= 40 Elderly with good performance status newly diagnosed MM all stages.	VAD x 4. Mobilize: C or GCSF alone. Conditioning: M 200. 12/40 on to double transplant.	0% TRM. Median OS not reached at 24 months f/u.	8	>20 in 5 days
Lerro	2003	57	N= 50 No previous alkylating agents stage 1 – 3.	VAD or pulse steroids or combo of 2. Mobilize: C + GCSF. Outpatient.	Median yield 4.88 (range .45 – 34.8) CD34 x 10^6/kg. Outpatient possible.		
Attal	2003	52	N= 399 Untreated MM	**RCT.** VAD x 3 or 4 cycles. Randomized to BM or PBSC mobilized with GCSF. Randomized to M 140 + TBI 8 Gy or M 140 followed by 1st BMT and then M 140 + TBI for 2nd BMT. IFN maintenance all groups.	OS 58 months double transplant vs 48 months single. TRM 4% single vs 6% double. Consider 2nd BMT if poor response first round.	Better hem recov ery with stem cells but no effect on EFS, RRate , or OS.	
Donato	2004	56	N= 18 Previously treated MM up to 8 prior regimens.	GCSF +- standard chemotherapy as mobilization. Topotecan, /C as conditioning regimen.	17% CR. Too early for survival data. 89% alive @ 12 months.	9	14
Horvath	2004	55	N= 34 Relapsed or advanced MM having received no greater than 1 prior chemo regimen	VAD x 3 induction, Mobilization: C + GMCSF. Conditioning: C/E first BMT with CD 34 selected cells followed by GMCSF and second harvest with B/M 140 and 2nd BMT. IFN maintenance	TRM 6%. OS 51.6 mos.		

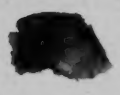
C = cyclophosphamide; M = Melphalan mg/m^2; TBI = total body irradiation; A = adriamycin; V = vincristine; D = dexamethasone; B= busulfan; E = etoposide; P= prednisone; GCSF = granulocyte colony stimulating factor; IFN = interferon; thal = thalidomide, dx = diagnosis; OS = overall survival; RR = response rate; CR = complete response, HR=hazard ratio

Author	Year	Age	Target population	Method	Result	ANC	PLT
Anagnosto-poulos	2004	53	N= 136 Untreated MM with or without initial response to induction chemo. Median time dx to transplant 7 months (range 2 – 30).	**Retrospective analysis.** Patient divided into three groups: A) pulse dexamethasone prior to BMT B) CVAD induction C) alkylating agent or anthracycline induction.	A- 39% CR B- 16% CR C- 27% CR Non-myelo-suppressive therapy induction an option.	10	14
Van Agthoren	2004	43	N= 261 Economic evaluation stage 2/3 previously untreated.	**RCT**. VAD x 3 or 4 cycles. Mobilization C + GCSF and two cycles M 70 + GCSF. Randomized to IFN maintenance or high dose C + TBI 9 Gy and BMT.	$48,800 chemo alone vs $57892 BMT OS 50 IFN vs 57 auto BMT.		
D'Sa	2004	50.5	N= 42 Primary refractory to VAD +/- other chemotherapy regimens stage 2-3 MM	E/methylprednisone/cytarabine/cisplatinum (ESHAP) post failure to respond to VAD versus C + GCSF for mobilizing. Conditioning M 200.	ESHAP mobilized to 7.3 x 10^6/kg vs cyclo at 2.4 x 10^6/kg. 87% collected minimum 2 x 10^6/kg ESHAP vs 67% with cylco. OS 62% at 4 years.		
Kumar (1)	2004		N= 107 Previously untreated MM median 6.5 months to transplant.	**Retrospective analysis.** Dexamethasone alone vs VAD as induction prior to BMT Mobilize C + GMCSF Consolidation: M 200 or M140 +- TBI 2 Gy.	26% CR for D vs 39% VAD. No difference survival 1 year post BMT.		
Kumar (2)	2004	56	N= 151 Primary refractory and chemo sensitive MM. Median time to transplant 6.5 months.	Induction with VAD. Mobilize: C + GMCSF. Consolidation: M 200 or M140 +- TBI 2 Gy.	20% CR for refractory vs 35% CR for chemo sensitive.		

C = cyclophosphamide; M = Melphalan mg/m^2; TBI = total body irradiation; A = adriamycin; V = vincristine; D = dexamethasone; B= busulfan; E = etoposide; P= prednisone; GCSF = granulocyte colony stimulating factor; IFN = interferon; thal = thalidomide, dx = diagnosis; OS = overall survival; RR = response rate; CR = complete response, HR=hazard ratio

Author	Year	Age	Target population	Method	Result	ANC	PLT
Murakami	2004	60	N= 150 Newly dx: 60 patients receiving transplant with 90 historical controls.	2 – 4 cycles of VAD. Mobilize: high dose C + GCSF or VP 16 + GCSF. Consolidation: M/MCNU/VP16 and V/M/mcnu/P vs historical controls on MP or C/P/V.	BMT OS 76 months vs 28 months with chemo alone.		
Novella	2004	57	N= 42 Untreated MM stage 1 – 3 to determine mobilizing without alkylating agent	Two groups consecutive patients 1) VAD x 2-4, C and GCSF versus 2) VAD x 2, Dex/C/E/cis platin (DCEP) + GCSF x 2 with PBSC collection post each DCEP.	87% 4 x 10^6/kg CD34+ count for both groups. Too early to report on differences in survival data.		
Levy	2005		N= 575 Meta-analysis total of 3 RCT trials with follow up > 5 years.	Attal 1996, Fermand , 1998, Fermand 1999 (abstract only)	No difference OS HR.887. Mean gain of 14.5 months.		
Putkonen	2005	59	N= 100 Untreated MM stage 1 – 3.	VAD x 3 or 4.Mobilize: C + GCSF. Consolidation with M 140 + TBI 12 Gy or M 200. 27 went on to double transplant. IFN maintenance	OS 60 months single transplant and 78+ months double transplant.		

Note. 1) Kumar, S., Lacy, M., Dispenzieri, A., Rajkumar, S., Fonseca, R., Geyer, S., et al. (2004), High dose therapy and autologous stem cell transplantation for multiple myeloma poorly responsive to initial therapy. *Bone Marrow Transplantation, 34*(2), 161-167.
2) Kumar, S., Lacy, M., Dispenzieri, A., Rajkumar, S., Fonseca, R., Geyer, S., et al. (2004). Single agent dexamethasone for pre-stem cell transplant induction therapy for multiple myeloma. *Bone Marrow Transplantation, 34*(6), 485-490.



C = cyclophosphamide; M = Melphalan mg/m^2; TBI = total body irradiation; A = adriamycin; V = vincristine; D = dexamethasone; B= busulfan; E = etoposide; P= prednisone; GCSF = granulocyte colony stimulating factor; IFN = interferon; thal = thalidomide, dx = diagnosis; OS = overall survival; RR = response rate; CR = complete response, HR=hazard ratio

Author	Year	Age	Target population	Method	Result	ANC	PLT
Moreau	2005	58	N= 219 Untreated MM stage 1 – 3. IFM 99-04.	**Multicenter RCT.** VAD x 3 or 4. Mobilize: GCS. First BMT with M 200. Randomized to 2nd BMT 1) dex + M 220 vs 2) M 200, Dex and anti IL6 monoclonal antibody (BE8)	TRM 5%. Median OS 51 months. No difference OS both arms.		
Cavo	2005	54	N= 200 Untreated MM stage 1 – 3.	**Case controlled** analysis. Thalidomide/D vs VAD for induction. Mobilize; C + GCSF.	7.85 x 106/kg for thalidomide-D, 10.5 x 106/kg in cyclo. VAD CR 8%, Thal-Dex 10%. Response rate thal dex 76%, VAD 52%. No survival data yet.		

C = cyclophosphamide; M = Melphalan mg/m^2; TBI = total body irradiation; A = adriamycin; V = vincristine; D = dexamethasone; B= busulfan; E = etoposide; P= prednisone; GCSF = granulocyte colony stimulating factor; IFN = interferon; thal = thalidomide, dx = diagnosis; OS = overall survival; RR = response rate; CR = complete response, HR=hazard ratio